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NEWS	3	Feb 06	Engineering Information Encompass files have new names
NEWS	4	Feb 16	TOXLINE no longer being updated
NEWS	5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS	6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS	7	May 07	DGENE Reload
NEWS	8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS	9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI

NEWS EXPRESS	July 11 CURRENT WINDOWS VERSION IS V6.0b, CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP), AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001
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FILE 'HOME' ENTERED AT 13:23:43 ON 24 JUL 2001

=> s 9-hydroxy risperidone
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FILE COVERS 1947 - 24 Jul 2001 VOL 135 ISS 5
FILE LAST UPDATED: 23 Jul 2001 (20010723/ED)

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```
=> s 9-hydroxy risperidone
       1387126 9
        282149 HYDROXY
           771 RISPERIDONE
L1          10 9-HYDROXY RISPERIDONE
                (9(W)HYDROXY(W)RISPERIDONE)

=> d l1 ibib abs hitstr 1-10
```

L1 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:415928 CAPLUS
DOCUMENT NUMBER: 133:275718
TITLE: Biotransformation of post-clozapine antipsychotics: pharmacological implications
AUTHOR(S): Caccia, Silvio
CORPORATE SOURCE: Instituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
SOURCE: Clin. Pharmacokinet. (2000), 38(5), 393-414
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 191 refs. The need to develop new antipsychotics that have

fewer motor adverse effects and offer better treatment of neg. symptoms has led to a new generation of drugs. Most of these drugs undergo extensive first-pass metab. and are cleared almost exclusively by metab., except for amisulpride whose clearance is largely due to urinary excretion. Risperidone has metabolic routes in common with ziprasidone but shows differences in regard to other main pathways: the benzisoxazole moiety of risperidone is oxidized by cytochrome P 450 (CYP) 2D6 to the active 9-hydroxyrisperidone, whereas the benzisothiazole of ziprasidone is primarily oxidized by CYP3A4, yielding sulfoxide and sulfone derivs. with low affinity for target receptors in vitro. Olanzapine, quetiapine and zotepine also have some common metabolic features. However, for the thienobenzodiazepine olanzapine a main metabolic route is direct conjugation at the benzodiazepine nucleus, whereas for the dibenzothiazepine quetiapine and the dibenzothiepine zotepine it is CYP3A4-mediated oxidn., leading to sulfoxidn., hydroxylation and dealkylation for quetiapine, but N-demethylation to the active nor-deriv. for zotepine. Although the promising benzisoxazole (iloperidone) and benzisothiazole (perospirone) antipsychotics share some metabolic routes with the structurally related available drugs, they too have pharmacol. relevant compd.-specific pathways. For some of the new antipsychotics we know the isoenzymes involved in their main metabolic pathways and the endogenous and exogenous factors that, by affecting enzyme activity, can potentially modify steady-state concns. of the parent drug or its metabolite(s), but we know very little about others (e.g. amisulpride isomers, nemonapride). For yet others, information is scare about the activity of the main metabolites and whether and how these contribute to the effect of the parent drug. Aging reduces the clearance of most antipsychotics, except amisulpride (which requires further evaluation) and ziprasidone. Liver impairment has little or no effect on the pharmacokinetics of olanzapine, quetiapine, risperidone (and **9-hydroxy-risperidone**) and ziprasidone, but information is lacking for amisulpride. Renal impairment significantly reduces the clearance and prolongs the elimination half-life of amisulpride and risperidone. Again, studies are still not available for some drugs (zotepine) and have focused on the parent drug for others (olanzapine, quetiapine, ziprasidone) despite the fact that renal impairment would be expected to lower the clearance of more polar metabolites. Addressing these issues may assist clinicians in the design of safe and effective regimens for this group of drugs, and in selecting the best agent for each specific population.

REFERENCE COUNT: 192
REFERENCE(S):
(1) Ahlenius, S; J Pharmacol Exp Ther 1997, V283, P1356 CAPLUS
(2) Andree, B; J Clin Psychopharmacol 1998, V18, P317 CAPLUS
(3) Andree, B; Psychopharmacology 1997, V131, P339 CAPLUS
(10) Aravagiri, M; Psychopharmacology 1998, V139, P356 CAPLUS
(11) Aravagiri, M; Ther Drug Monit 1997, V19, P307 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 2 OF 10 CAPLUS

ACCESSION NUMBER: 2000:325976 CAPLUS
DOCUMENT NUMBER: 132:329415
TITLE: Risperidone drug monitoring: a useful clinical tool?
AUTHOR(S): Odou, Pascal; Levron, J. C.; Luyckx, M.; Brunet, C.; Robert, Hugues
CORPORATE SOURCE: Service Pharmacie, EPSM Lille Metropole, Armentieres, Fr.
SOURCE: Clin. Drug Invest. (2000), 19(4), 283-292
CODEN: CDINFR; ISSN: 1173-2563
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Risperidone is an atypical antipsychotic drug that has been marketed in France since 1996. Therapeutic failures have been obsd. with risperidone. Objective: To investigate whether interactions with the cytochrome P 450 (CYP) isoenzymes implicated in risperidone metab. could explain these treatment failures. Design and Setting: This was a retrospective study of clin. and drug monitoring data from 50 patients treated by five psychiatrists in northern France. Methods: The concn. of active drug (risperidone + **9-hydroxy-risperidone**) in serum was evaluated by high performance liq. chromatog. and radio receptor assay. Clin. efficacy was assessed by the global improvement (CGI2) item of the Clin. Global Impression rating scale. Results: Statistical anal. revealed a significant increase in efficacy when the serum concn. of active drug was between 25 and 150 .mu.g/L compared with when it was out of this range. Carbamazepine, a CYP3A4 inducer, dramatically decreased the concn. of the active moiety of risperidone; on the contrary, CYP3A4 inhibitors (alprazolam and valproic acid) increased the concn. of active drug. The metab. of risperidone by CYP3A4 did not lead to the formation of metabolite(s) with anti-D2 dopaminergic activity. Drugs interacting with CYP2D6 altered the risperidone/**9-hydroxy-risperidone** ratio but did not change the total amt. of active drug. Conclusions: We have established a therapeutic range for risperidone. CYP3A4 is a major pathway for risperidone metab. Consideration of these factors in clin. practice should lead to improved outcomes for patients treated with risperidone.

REFERENCE COUNT: 35
REFERENCE(S):
(1) Aravagiri, M; Pharmacopsychiatry 1998, V31, P102 CAPLUS
(14) Fang, J; Naunyn Schmiedebergs Arch Pharmacol 1999, V359(2), P147 CAPLUS
(15) Fischer, V; J Pharmacol Exp Ther 1992, V260(3), P1355 CAPLUS
(18) Koley, A; Biochem Pharmacol 1997, V53(4), P455 CAPLUS
(20) Leysen, J; Psychopharmacology 1993, V112, PS40 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:746542 CAPLUS
DOCUMENT NUMBER: 132:189311
TITLE: Lack of drug interactions between mirtazapine and risperidone in psychiatric patients: a pilot study
AUTHOR(S): Loonen, A. J. M.; Doorschot, C. H.; Oostelbos, M. C. J. M.; Sitsen, J. M. A.
CORPORATE SOURCE: Delta Psychiatric Hospital, Poortugaal, 3170 DZ, Neth.

SOURCE: Eur. Neuropsychopharmacol. (1999), 10(1), 51-57
CODEN: EURNE8; ISSN: 0924-977X
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An open-label, non-randomized, pilot study has been performed in inpatients in need of treatment with an antipsychotic (risperidone) and an antidepressant (mirtazapine) with the objective to preliminarily assess a possible pharmacokinetic interaction and the tolerability of this combination. A 1-4-wk single drug treatment phase (risperidone 1-3 mg bid or mirtazapine 30 mg nocte) was followed by a 2-4-wk combined drug treatment phase at unchanged doses. Twelve patients were enrolled, nine of whom were treated with risperidone in the single drug phase. Results of plasma level measurements are available for six patients and indicate that adding mirtazapine to risperidone does not alter steady-state plasma concns. of risperidone and its 9-hydroxy metabolite. Data from one patient suggest that adding risperidone to mirtazapine does not result in clin. relevant changes in plasma concns. of either compd. The combination was well tolerated and no major or relevant adverse events were obsd. Adding risperidone to mirtazapine probably does not necessitate a change of the dosage of either drug, but more extensive investigations are needed.

REFERENCE COUNT: 23
REFERENCE(S):
(1) Berendsen, H; Psychopharmacology 1998, V135, P284 CAPLUS
(3) Davies, A; Clin Ther 1998, V20, P58 CAPLUS
(6) De Boer, T; Eur J Pharmacol 1994, V253, PR5 CAPLUS
(7) Fang, J; Naun Schmied Arch Pharmacol 1999, V359, P147 CAPLUS
(8) Gram, L; Ther Drug Mon 1982, V4, P17 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:344849 CAPLUS
DOCUMENT NUMBER: 130:357192
TITLE: Aqueous suspensions of submicron 9-hydroxyrisperidone fatty acid esters
INVENTOR(S): Francois, Marc Karel Jozef; Dries, Willy Maria Albert Carlo; Basstanie, Esther Dina Guido
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925354	A2	19990527	WO 1998-EP7321	19981110
WO 9925354	A3	19990819		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,

NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9920491	A1	19990607	AU 1999-20491		19981110
EP 1033987	A2	20000913	EP 1998-965159		19981110
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO					
BR 9814202	A	20000926	BR 1998-14202		19981110
NO 2000002278	A	20000628	NO 2000-2278		20000428
PRIORITY APPLN. INFO.:			EP 1997-203568	A	19971117
			WO 1998-EP7321	W	19981110

OTHER SOURCE(S): MARPAT 130:357192

AB An aq. suspension suitable as a depot injection for i.m. or s.c. administration of a **9-hydroxy-risperidone** fatty acid ester or a salt, or a stereoisomer or a stereoisomeric mixt. thereof in submicron form is described. The depot injection is useful in the treatment of psychosis, schizophrenia, schizo-affective disorders, non-schizophrenic psychoses, behavioral disturbances assocd. with neurodegenerative disorders, e.g. in dementia, behavioral disturbances in mental retardation and autism, Tourette's syndrome, bipolar mania, depression, and anxiety. A formulation was prepd. contg. 9-hydroxyrisperidone palmitate 7.02, polysorbate 20 1.1, Na CM-cellulose (a suspending agent) 1.0, benzyl alc. (a preservative) 1.5, Na2HPO4 0.6, and water up to 100%, resp.

L1 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1999:136683 CAPLUS
DOCUMENT NUMBER:	130:246950
TITLE:	Therapeutic drug monitoring of risperidone using a new, rapid HPLC method: Reappraisal of interindividual variability factors
AUTHOR(S):	Balant-Gorgia, Androniki E.; Gex-Fabry, Marianne; Genet, Chantal; Balant, Luc P.
CORPORATE SOURCE:	Therapeutic Drug Monitoring Unit, Geneva University Hospitals, Geneva, Switz.
SOURCE:	Ther. Drug Monit. (1999), 21(1), 105-115 CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER:	Lippincott Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Because of the enormous gap between premarketing studies in phys. healthy subjects and clin. practice in patients, the present study reconsidered interindividual variability factors affecting risperidone concns. under routine therapeutic drug monitoring conditions. The study included 92 patients, 27% of whom were 70 yr or older. The patients received risperidone orally (dose range, 0.5-11 mg per day) and had concns. of risperidone and the active metabolite **9-hydroxy-risperidone** measured at steady state by a new, rapid, and sensitive method of high-performance liq. chromatog. (HPLC). After normalization to a dose of 4 mg/day, median concns. were 2.9 ng/mL (80% range, 0.9-27.9 ng/mL) for the parent compd. and 24.1 ng/mL (80% range, 12.0-57.6 ng/mL) for the metabolite. When considering linear regression models, age was identified as a major source of interindividual variability, with expected increases of 340% and 220% for concns. of parent compd. and metabolite, with age increasing from 20 to 80 yr. Body

wt. provided an addnl. significant contribution to the variability of **9-hydroxy-risperidone** concn., a 20-kg higher body wt. assocd. with a concn. decrease of 23%. Serotonin-specific reuptake inhibitor (SSRI) comedication (fluoxetine, two patients; citalopram, two patients; paroxetine, one patient; fluvoxamine, one patient) was significantly assocd. with 4.6-fold higher concns. of parent compd., in keeping with an inhibitory action on CYP2D6 enzyme. Significantly higher concns. of **9-hydroxy-risperidone** (+ 29%) were also obsd. in the 17 patients with biperiden comedication. Therapeutic drug monitoring data, collected in patients representative of the population for which the drug was intended, allowed us to quantify the dose redn. needed in elderly patients and thus provided valuable information in addn. to the one collected during premarketing studies performed with strict inclusion and exclusion criteria.

REFERENCE COUNT: 31

REFERENCE(S):
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(7) Ereshefsky, L; Clin Chem 1988, V34, P863 CAPLUS
(8) Ereshefsky, L; J Clin Psychiatr 1996, V57, P12 CAPLUS
(11) Gex-Fabry, M; Ther Drug Monit 1995, V17, P39 CAPLUS
(12) Gex-Fabry, M; Ther Drug Monit 1997, V19, P1 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:671753 CAPLUS
DOCUMENT NUMBER: 130:32658

TITLE: Distribution after repeated oral administration of different dose levels of risperidone and **9-hydroxy-risperidone** in the brain and other tissues of rat

AUTHOR(S): Aravagiri, Manickam; Yuwiler, Arthur; Marder, Stephen R.
CORPORATE SOURCE: Neurobiochemistry Lab, West Los Angeles Veterans Administration Medical Center, Los Angeles, CA, 90073, USA

SOURCE: Psychopharmacology (Berlin) (1998), 139(4), 356-363
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rats were treated with daily oral doses of 1, 4, and 6 mg/kg risperidone (RSP) and its metabolite, **9-hydroxy-risperidone** (9-OH-RSP), for 15 consecutive days. Concns. of RSP and 9-OH-RSP were measured in plasma, brain, liver, kidney, lungs and fat tissue by high-performance liq. chromatog. with electrochem. detection. Non-specific distribution of RSP and 9-OH-RSP in various brain regions was also studied after administration of 6 mg/kg per day oral dose for 15 days. After RSP treatment, concns. of 9-OH-RSP were higher than those of RSP in plasma and tissues except in brain, where both compds. were present in nearly equal concns. Similarly, after 9-OH-RSP treatment, levels of

9-OH-RSP were higher than levels of either RSP or 9-OH-RSP or the sum of RSP and 9-OH-RSP levels measured after treatment with RSP. There was a moderate relation between RSP dose and tissue levels of RSP and 9-OH-RSP (all rs .gtoreq. 0.62), except in fat. There was also a strong relation between the dose and tissue levels of 9-OH-RSP (all rs .gtoreq. 0.68). A significant relation was found between plasma levels of RSP and brain levels of RSP and 9-OH-RSP (all rs .gtoreq. 0.57) after treatment with RSP. After 9-OH-RSP treatment, a much stronger relation was obsd. between plasma and brain 9-OH-RSP levels (rs .gtoreq. 0.90). The plasma concns. of RSP and 9-OH-RSP appear to reflect their concns. in brain. The tissue-to-plasma ratios of RSP and 9-OH-RSP were relatively low compared to other antipsychotics. In liver, kidney and lung the tissue to plasma ratio for RSP and 9-OH-RSP after treating with RSP ranged from 0.85 to 3.4. The brain to plasma ratio for RSP and 9-OH-RSP was several-fold lower than that in peripheral tissues. After RSP administration, the mean brain to plasma level ratio for RSP was 0.22, and for 9-OH-RSP to it was 0.04. The brain to plasma ratio of 9-OH-RSP after giving 9-OH-RSP was similarly low (0.04). The low brain/plasma ratio of high potency RSP and 9-OH-RSP may in part be due to their low lipophilicity, log and 2.32, resp., resulting in limited non-specific accumulation in brain tissue.

REFERENCE COUNT: 24

REFERENCE(S):
(1) Aravagiri, M; Neuropsychopharmacology 1995, V13, P235 CAPLUS
(4) Baldessarini, R; Neuropsychopharmacology 1993, V9, P117 CAPLUS
(5) Blin, O; J Clin Psychopharmacol 1996, V16, P38 CAPLUS
(12) Janssen, P; J Pharmacol Exp Ther 1988, V244, P685 CAPLUS
(13) Leysen, J; J Pharmacol Exp Ther 1988, V247, P661 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:466087 CAPLUS
DOCUMENT NUMBER: 129:239388
TITLE: Plasma concentrations of risperidone and its 9-hydroxy metabolite and their relationship to dose in schizophrenic patients: simultaneous determination by a high performance liquid chromatography with electrochemical detection
AUTHOR(S): Aravagiri, M.; Marder, S. R.; Wirshing, Donna; Wirshing, W. C.
CORPORATE SOURCE: Psychopharmacology Unit, University of California of Los Angeles, Los Angeles, CA, USA
SOURCE: Pharmacopsychiatry (1998), 31(3), 102-109
CODEN: PHRMEZ; ISSN: 0176-3679
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A simple, sensitive and accurate method for the simultaneous detn. of risperidone (RSP) and its 9-hydroxy metabolite (9-OH-RSP) in human plasma is described. The relationship between dose of RSP and the plasma concn.

of RSP and 9-OH-RSP in a clin. situation is discussed. Both compds. were isolated from plasma by a simple one-step liq.-liq. extn. with 15% methylene chloride in pentane. High-performance liq. chromatog. sepns. were made on a cyano column and the compds. were detected by electrochem. detector. The method had sufficient sensitivity to det. RSP and 9-OH-RSP accurately concns. as low as 0.25 ng/mL when 1 mL of plasma is used for the anal. The assay detns. were accurate, precise and consistent with a coeff. of variation less than 15%. Commonly co-administered drugs and other antipsychotics did not interfere with the anal. of either RSP or 9-OH-RSP There were large variations in inter- and intra-individual values of plasma concns. of RSP and 9-OH-RSP. The 9-OH-RSP appears to be the major circulating active moiety and its plasma concns. were, on the av. 22 fold higher than that of RSP in schizophrenic patients treated with RSP. The ratio of RSP/9-OH-RSP concns. suggested that three of the patients may have deficiency in cytochrome P 450 enzyme CYP 2D6. The plasma concns. of RSP showed a weak relationship with the administered daily oral dose ($r = 0.4684$, $p = 0.01$, $n = 215$). However, there was a good relationship between the daily dose of RSP and the plasma concn. of 9-OH-RSP ($r = 0.6654$, $p = 0.01$, $n = 280$) or the total active moiety, sum of RSP and 9-OH-RSP concns. ($r = 0.7041$, $p = 0.0005$, $n = 280$). The measurement of the total active moiety in plasma of schizophrenic patients may be useful for assessing the relationship between dose and plasma concn. and dose and clin. outcome of patients rather than measuring RSP alone.

L1 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:449591 CAPLUS
DOCUMENT NUMBER: 121:49591
TITLE: Plasma protein binding of risperidone and its distribution in blood
AUTHOR(S): Mannens, Geert; Meuldermans, Willem; Snoeck, Eric; Heykants, Joseph
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinet., Janssen Res. Found., Beerse, B-2340, Belg.
SOURCE: Psychopharmacology (Berlin) (1994), 114(4), 566-72
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The plasma protein binding of the new antipsychotic risperidone and of its active metabolite **9-hydroxy-risperidone** was studied in vitro by equil. dialysis. Risperidone was 90.0% bound in human plasma, 88.2% in rat plasma and 91.7% in dog plasma. The protein binding of **9-hydroxy-risperidone** was lower and averaged 77.4% in human plasma, 74.7% in rat plasma and 79.7% in dog plasma. In human plasma, the protein binding of risperidone was independent of the drug concn. up to 200 ng/mL. The binding of risperidone increased at higher pH values. Risperidone was bound to both albumin and .alpha.1-acid glycoprotein. The plasma protein binding of risperidone and **9-hydroxy-risperidone** in the elderly was not significantly different from that in young subjects. Plasma protein binding differences between patients with hepatic or renal impairment and healthy subjects were either not significant or rather

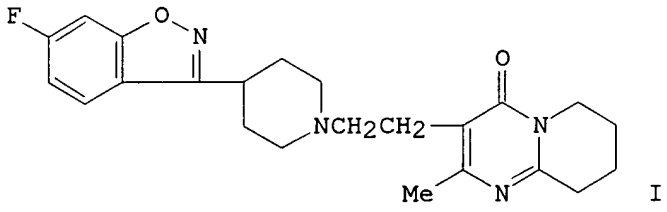
small. The blood to plasma concn. ratio of risperidone averaged 0.67 in man, 0.51 in dogs and 0.78 in rats. Displacement interactions of risperidone and **9-hydroxy-risperidone** with other drugs were minimal.

L1 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:400189 CAPLUS
DOCUMENT NUMBER: 121:189
TITLE: Regional brain distribution of risperidone and its active metabolite **9-hydroxy-risperidone** in the rat
AUTHOR(S): van Beijsterveldt, Ludy E. C.; Geerts, Rita J. F.; Leysen, Josee E.; Megens, Anton A. H. P.; Van den Eynde, Hilde M. J.; Meuldermans, Willem, E. G.; Heykants, Jozef J. P.
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinet., Janssen Res. Found., Beerse, B-2340, Belg.
SOURCE: Psychopharmacology (Berlin) (1994), 114(1), 53-62
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Risperidone is a new benzisoxazole antipsychotic. **9-Hydroxy-risperidone** is the major plasma metabolite of risperidone. The pharmacol. properties of **9-hydroxy-risperidone** were studied and appeared to be comparable to those of risperidone itself, both in respect to the profile of interactions with various neurotransmitters and its potency, activity, and onset and duration of action. The absorption, metabolically formed **9-hydroxy-risperidone** and total radioactivity were studied in the male Wistar rat after single s.c. administration of radiolabeled risperidone at 0.02 mg/kg. Concns. were detd. by HPLC sepn., and off-line detn. of the radioactivity with liq. scintillation counting. Risperidone was well adsorbed. Max. plasma concns. were reached at 0.5-1 h after s.c. administration. Plasma concns. of **9-hydroxy-risperidone** were higher than those of risperidone from 2 h after dosing. In plasma, the apparent elimination half-life of risperidone was 1.0 h, and mean residence times were 1.5 h for risperidone and 2.5 h for its 9-hydroxy metabolite. Plasma levels of the radioactivity increased dose proportionally between 0.02 and 1.3 mg/kg. Risperidone was rapidly distributed to brain tissues. The elimination of the radioactivity from the frontal cortex and striatum-brain regions with high concns. of 5-HT2 or dopamine D2 receptors-became more gradual with decreasing dose levels. After a s.c. dose of 0.02 mg/kg, the ED50 for central 5-HT2 antagonism in male rats, half-lives in frontal cortex and striatum were 3-4 h for risperidone, whereas mean residence times were 4-6 h for risperidone and about 12 h for **9-hydroxy-risperidone**. These half-lives and mean residence times were 3-5 times longer than in plasma and in cerebellum, a region with very low concns. of 5-HT2 and D2 receptors. Frontal cortex and striatum to plasma concn. ratios increased during the expt. The distribution of **9-hydroxy-risperidone** to the different brain regions, including frontal cortex and striatum, was more limited than that of risperidone itself. This indicated that **9-hydroxy-risperidone** contributes to the in vivo activity of risperidone, but to a smaller extent than would be predicted from plasma levels. AUCs of both active compds. in frontal cortex and striatum were 10-18 times higher than those

in cerebellum. No retention of metabolites other than **9-hydroxy-risperidone** was obsd. in any of the brain regions investigated.

L1 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:235292 CAPLUS
DOCUMENT NUMBER: 120:235292
TITLE: Absorption, metabolism, and excretion of risperidone in humans
AUTHOR(S): Mannens, Geert; Huang, May Lynn; Meuldermans, Willem; Hendrickx, Jan; Woestenborghs, Robert; Heykants, Joseph
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinet., Janssen Res. Found., Beerse, B-2340, Belg.
SOURCE: Drug Metab. Dispos. (1993), 21(6), 1134-41
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The absorption, metab., and excretion of the novel antipsychotic risperidone (I) was studied in three healthy male subjects. One week after a single oral dose of 1 mg [14C]I 70% of the administered radioactivity was recovered in the urine and 14% in the feces. Unchanged I was mainly excreted in the urine and accounted for 30, 11, and 4% of the administered dose in the poor, intermediate, and extensive metabolizer of debrisoquine, resp. Alicyclic hydroxylation at the 9-position of the tetrahydro-4H-pyrido[1,2-a]-pyrimidin-4-one moiety was the main metabolic pathway. The active metabolite **9-hydroxy-risperidone** accounted for 8, 22, and 32% of the administered dose in the urine of the poor, intermediate, and extensive metabolizer, resp. Oxidative N-dealkylation at the piperidine nitrogen, whether or not in combination with the 9-hydroxylation, accounted for 10-13% of the dose. In methanolic exts. of feces, I and benzisoxazole-opened I and hydroxylated metabolites were detected. **9-Hydroxy-risperidone** was by far the main plasma metabolite. The sum of I and **9-hydroxy-risperidone** accounted for the largest part of the plasma radioactivity in the three subjects. Although the debrisoquine-type genetic polymorphism plays a distinct role in the metab. of I, the pharmacokinetics of the active fraction (i.e. I plus **9-hydroxy-risperidone**) remained similar among the three subjects.